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Fertility-sparing treatment in female genital cancer and breast cancer

Leczenie nowotworów złośliwych żeńskiego narządu rodnego i piersi z zachowaniem możliwości prokreacji

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Abstract

Postponed motherhood is the reason why many women are diagnosed with cancer before they make the decision to conceive a child, but only a small number of the affected patients will receive any information about treatment-related infertility.

As far as female genital cancer is concerned, cervical cancer continues to be the most frequently diagnosed malignancy in women of childbearing age. In its early stages, it can be treated with surgical procedures which spare the genitals, i.e. surgical conization and vaginal radical trachelectomy with laparoscopic lymphadenectomy. The advantages of these procedures have been observed in our experience. Also, a successful conservative 6-month treatment of endometrial cancer limited to the mucous membrane with progestagens following curettage of the uterine cavity has been reported in the literature.

This paper also presents our own experience with fertility-sparing surgical treatment of ovarian cancer with borderline malignancy and invasive IA stage. Breast cancer affects over 7% of all cancer patients under the age of 40. Pregnancy after breast cancer treatment has been shown to develop properly and both, pregnancy and breast-feeding have no influence on cancer relapse. Protective shields for the adnexa or relocation of the ovaries should be used during radiotherapy in patients who wish to preserve their fertility. In case of chemotherapy, application of GnRH analogs has shown promising results in preservation of the ovarian function. Also, the development of new assisted reproductive technology has offered an increasing number of alternatives for young cancer patients who wish to preserve their fertility.

Key words: **cervical cancer** / **endometrial cancer** / **ovarian cancer** / **breast cancer** / / **fertility preservation** /

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Streszczenie

Przesuwanie macierzyństwa na późniejsze lata sprawia, że u wielu kobiet wystąpienie choroby nowotworowej często wyprzedza decyzję o macierzyństwie. Niestety, tylko część pacjentek z rozpoznanym nowotworem złośliwym zlokalizowanym nierzadko poza narządem rodnym otrzymuje informację na temat możliwości niepłodności związanej z leczeniem procesu nowotworowego.

Wśród nowotworów złośliwych narządu rodnego jednym z najczęstszych występujących w okresie zdolności do prokreacji jest rak szyjki macicy. Jego wczesne postacie można leczyć chirurgicznie oszczędzając narząd rodny tj. wykonując chirurgiczną konizacją lub radykalną pochwową trachelektomię z laparoskopową limfadenektomią. O wartości takiego postępowania świadczą nasze własne doświadczenia. Istnieją także doniesienia o zachowawczym leczeniu progestagenami w sytuacji raka endometrium ograniczonego do błony śluzowej, po uprzednim wyłyżeczkowaniu jamy macicy.

W pracy przedstawiono doświadczenia (również własne) w leczeniu chirurgicznym raka jajnika o granicznej złośliwości i w stopniu zaawansowania klinicznego IA zachowując prokreacje. Około 7% raka piersi dotyczy kobiet poniżej 40 roku życia. Wskazano, że ciąża po leczeniu raka piersi rozwija się prawidłowo. Podobnie, zarówno ciąża jak i karmienie zdrową piersią nie mają wpływu na wzrost ryzyka wznowy raka piersi. Przy stosowaniu radioterapii w zależności od lokalizacji nowotworu u kobiet pragnących zachować płodność należy stosować osłony na przydatki lub wykonać relokację jajników. W razie konieczności stosowania chemioterapii obiecujące wyniki w oszczędzeniu funkcji rozrodczych jajników daje zastosowanie w trakcie jej trwania analogów GnRH. Coraz częściej również w tych trudnych sytuacjach bezpieczne rozwiązania oferują nowe techniki medycyny wspomaganego rozrodu.

Słowa kluczowe: **rak szyjki macicy** / **rak endometrium** / **rak jajnika** / **rak piersi** / / **zachowanie płodności** /

Delayed motherhood is often a reason why many women may develop cancer before they decide to conceive [1, 2, 3, 4]. As the incidence of malignant cancer increases with age, it affects an increasing number of pregnant women as well as nulliparas [1, 2, 6, 7, 8]. Numerous women who suffered from cancer, not infrequently in childhood, often express their desire to bear children [2, 3, 4, 5, 6].

Moreover, the issue of oncologic treatment applies to many young women who still have not made the decision about their possible motherhood. A study in over 1000 women diagnosed with cancer between the ages of 18 to 40 years showed that only under 60% of them received information about the risk of treatment-related infertility from their oncologists, and only about 5% were referred to a consult with a reproductive endocrinologist [9]. Needless to say, the decision about initiating fertility-sparing treatment should be established at the time of diagnosis, before any oncologic treatment is started.

In 2012, over 10% of female cancers diagnosed in the USA affected women of childbearing age [7, 8]. The occurrence of cancer during pregnancy has been estimated at 1/1000 pregnant women globally. Premalignant cervical lesions, as well as cervical cancer and breast cancer, are among the most frequent malignancies detected during pregnancy, with melanomas and hematologic cancers as significantly less common [1]. Cervical cancer remains to be the most frequently diagnosed neoplasm of the genital tract in women of childbearing age [2, 3, 10, 11]. Approximately 20% of cervical cancer patients are up to 40 years of age, with early stage cervical cancer, i.e. carcinoma in situ and stage IA cancer, diagnosed in over 60% of women in that age group [10]. The long and multi-step process of carcinogenesis within the cervix, from CIN 1 to invasive cancer (often lasting for many years), the ability to observe the cervix, and two non-invasive diagnostic methods of cytology and colposcopy allow to detect both, premalignant lesions and a large proportion of cervical cancer in its preclinical stage (IA) and early clinical stage (IB1 with lesions of <2cm in diameter). In these stages of cervical cancer, when metastases are an unexpected occurrence and only isolated cancer cells are found in the lymph nodes, genital-sparing surgical treatment, i.e. surgical conization and vaginal radical trachelectomy with laparoscopic lymphadenectomy, may be implemented. The advantages of such procedures have been reported by numerous authors [12, 13, 14]. In our research, 76.5% of women after surgical conization achieved pregnancy and 90% delivered at term, whereas 50% of women after vaginal radical trachelectomy with laparoscopic lymphadenectomy achieved pregnancy and 50% delivered at term. It should be emphasized that pregnancy after vaginal radical trachelectomy should be regarded as a high-risk pregnancy, with higher incidence of chorioamnionitis and preterm rupture of membrane (PROM), often resulting in premature delivery. Some clinicians attempted to implement genital-sparing treatment in subjects with more advanced cervical cancer, e.g. clinical stages IB2 and IIA, first using chemotherapy (platinum with paclitaxel), followed by conization or cervical amputation. However, in light of oncologic effectiveness, this procedure seems risky [4].

As far as the other female genital tract neoplasms are concerned, reports (45 studies) about treatment options with progestogens in endometrial cancer limited to the mucous membrane, i.e. IA clinical stage advancement according to previous FIGO classification (1988), have been published. Notably, endometrial cancer during childbearing years is rare. Thus, data on progestogen treatment of both, endometrial hyperplasia and stage I clinically advanced adenocarcinoma in women who wish to preserve fertility are extremely limited (approximately 300 cases) [15].

In our center, we observed 2 patients (aged 41 and 43 years), who wished for medroxyprogesterone to be introduced for 6 months after curettage of the uterine cavity. Control curettage

with subsequent histology after this period of time did not reveal any neoplastic processes but neither one of them became pregnant.

Ovarian cancer in young women, even young girls, who wish to preserve fertility occurs much more frequently than endometrial cancer. In our study, a diagnosed and treated group of 26 young women (aged 18-29 years) with a unilateral, borderline malignancy ovarian cancer, as well as a group of 17 young women (aged 16-23 years) with stage I clinically advanced invasive cancer also limited to one ovary, show possibility of organ-sparing surgical treatment with fertility preservation.

In all cases with a unilateral tumor of borderline malignancy the procedure was as follows: after incision into the cavity, peritoneal lavage was performed and taken for cytological examination, unilateral salpingo-ooporectomy, random biopsy of the second ovary for histologic examination, and inspection of the pelvis minor and abdominal cavity. Neither cytological examination of the lavage fluid nor histologic examination of the biopsied samples in the second ovary showed any cancer cells.

Surgical treatment in the second group, with stage I clinically advanced invasive cancer of one ovary (stage IA), consisted of peritoneal lavage taken for cytological examination, followed by unilateral salpingo-ooporectomy and tumor removal with the capsule intact without any damage, omentectomy, appendectomy, pelvic and paraaortic lymphadenectomy, and a random biopsy of the second ovary for histologic examination. Definitive histological examination showed metastasis of cancer cells to the lymph nodes (stage IIIA1) in only one case.

During the observation period of 2-7 years, there were no cases with any recurrence of neoplastic process in either of the two groups.

In the group with borderline malignancy, 19 women decided to become pregnant and 14 (73.7%) conceived and gave birth at term. In the group with stage I clinically advanced cancer, out of the 11 women who wanted to become pregnant shortly after the operation, 8 (72.7%) managed to conceive and deliver at term. Therefore, fertility-sparing surgical treatment of ovarian cancer with both, borderline malignancy and stage IA invasiveness gives good results in terms of subsequent procreation, what is consistent with reports of other authors [16, 17]. In cases where fertility-sparing surgical treatment is implemented with subsequent chemotherapy, women who wish to preserve fertility should have oocytes or ovarian tissue sampled and frozen in designated centers prior to chemotherapy [16, 17].

Regardless of the fact that breast cancer more frequently affects postmenopausal women, about 7% of the cases are diagnosed under the age of 40, constituting about 40% of all malignant cancers found in women of childbearing age [18]. The decision to become pregnant after breast cancer treatment presents a great challenge, mainly due to the fact that many of those cancers appear as the effect of hormonal stimulation. Thus, alongside women who are optimistic about pregnancy after breast cancer treatment, there is a group of patients who oppose pregnancy after cancer treatment or remain undecided [19].

Numerous analyses of the existing data on the impact of pregnancy on cancer recurrence failed to demonstrate its negative consequences on disease relapse or recurrence. This statement is also true with regard to cancers that possess a hormonal receptor status or BRCA 1/2 mutation carrier status [18, 20, 21].

Also, the same authors believe that there is no reason to limit breastfeeding with the healthy breast after treatment completion. Moreover, breastfeeding is a protective factor against the development of breast cancer.

Independently of tumor location, i.e. not only within the genitals but also in other parts of the body, protective shields for the adnexa or laparoscopic relocation of the ovaries (most frequently to the area of paracolic gutters) should be done in women wishing to preserve their fertility if radiotherapy is applied. The prognosis depends on changes in the vascularization of the ovary and the degree of radiation scatter. Sometimes both, the adnexa and the uterus should be shielded as radiation can lead to reduction of the uterine mass, and is related to complications in future pregnancy.

Recent reports have confirmed previous, empirically employed, attempts of preserving adnexal function from the undesirable effects of chemotherapeutic drugs by using GnRH analogues [22, 23]. However, this method is characterized by limited effectiveness – the estimated improvement in the function of the ovaries does not exceed 10% (2013 ESMO recommendations) [1, 23].

In cases when none of the aforementioned techniques can be used, or if there is a reasonable suspicion of a possible lack of their effectiveness, the latest developments in the assisted reproductive technology may offer significant help. They include both, freezing the embryos and oocytes, as well as ovarian tissue fragments. Embryo freezing is the technique of choice if the affected woman has a partner with whom she plans to start a family. Currently, this method is fully approved and reimbursed by the Ministry of Health. In cases when the woman does not have a partner with whom she wishes to have children, the solution is to freeze mature oocytes. Depending on patient age and the timeframe in which oncologic treatment should begin, the oocytes can be retrieved without initial stimulation, and their maturation guaranteed in laboratory settings (in vitro maturation – IVM). However, this technique is associated with lower (estimated only at about 10%) effectiveness than retrieving the oocytes after the initial stimulation [7]. Significantly better results of attaining pregnancy (estimated at about 30-35%) are achieved through the vitrification technique. In contrast to the previously used slow freezing, nowadays the mature oocytes in the M2 stage are rapidly frozen in liquid nitrogen [24]. The method that currently offers most promise involves freezing the entire fragments of the ovarian tissue. Although this technique is still considered as an experimental method, to the best of our knowledge, a few dozen cases achieving pregnancy in this method have been described so far, the initial results are promising and give a chance for offspring to 30% of women who decide to choose this technique [25, 26].

Ultimately, it should be noted that cancer patients who wish to preserve fertility should be given comprehensive information about the safety of reproductive organ-sparing techniques, as well as the possibility of using other fertility-sparing methods before oncologic treatment commences. In cases of early-stage cancer within the reproductive tract, the principles of organ-sparing surgical treatment, as well as the risk of potential cancer recurrence, should be discussed.

In cases of cancers located elsewhere and requiring radiation and/or chemotherapy, the possibility of shielding the

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reproductive organs against the undesired effects of radiation or chemotherapeutic agents should be presented to the affected women. It should be noted that recent years have brought new methods of reproductive medicine that offer hope for motherhood to those women in whom the previously described methods of preserving fertility cannot be applied.

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